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EXAMINER	
KELLY, ROBERT M	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,010	LIVELY ET AL.	
	Examiner	Art Unit	
	ROBERT M. KELLY	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,12-32,37-46 and 67-83* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 12-32, 37-46, and 67-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response and amendment of 11/3/08 have been entered.

Claims 8-11 and 47-66 are cancelled.

Claims 1, 25, and 67 are amended.

Claims 72-83 are newly added.

Claims 1-7, 12-32, 37-46, and 67-83 are presently pending.

Election/Restrictions

Applicant has cancelled all claims drawn to non-elected inventions.

Claims 1-7, 12-32, 37-46, and 67-83 are presently considered.

Claim Status, Cancelled Claims

In light of the cancellation of Claims 8-11 and 47-66, all rejections and/or objections to such claims are rendered moot, and thus, are withdrawn.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or

provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/414,097, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application.

The 60/414,097 Application fails to provide any of the data or information available in present Example 4 for support. Such support is the only support provided for the stability of these formulations. Hence, Applicant is denied priority to such document.

Claim Rejections - 35 USC § 112 – Clarity

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 12-32, 37-46, and 67-83 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 25, and 67 each contain the newly-amended generic limitation "wherein the particles suitable for delivery have a half-life of greater than 20 days at 40[degrees]C." Such is so broad as to be undefined. The conditions in which define the system depend on the fluid the particles are within, the pressure of the system, the exposure to enzymes, acids, bases, and other chemical and biochemical components, as well the length of the DNA, and other components not

mentioned (e.g., trehalose? sucrose? salts?) present in the system. Hence, the Artisan would not know when the claim was being infringed from such generic limitation as the system is essentially only partly defined.

Claims 1, 25, and 67 are not clear for their metes and bounds. The present amendment appears to indicate that either a composition is claimed in which particles have a specific half-life, or, under an alternative interpretation, appears to claim only those particles which are suitable for delivery and are at least half-active after 20 days at 40 deg. C. Hence, these alternative, non-coextensive interpretations, lead to a lack of clarity such that the Artisan would not understand when he or she is infringing the claim.

Claim 81 is self-dependent and hence the scope which is intended is not determined. Moreover, due to the various new chains of dependencies it is simply impossible to guess, so no further consideration is provided for the substance of such claim, except in that it must depend from another claim, and if every other claim is so-rejected under a single basis, it must also be so-rejected.

Claims 1-7, 12-32, 37-46, and 67-83 are rejected for depending from a rejected base claim and not overcoming the lack of clarity.

Claim Rejections - 35 USC § 112 – New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 12-32, 37-46, and 67-83 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for comprising new matter. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 25, and 67 each contain the newly-amended generic limitation "wherein the particles suitable for delivery have a half-life of greater than 20 days at 40[degrees]C." The balance of the claims depend from these claims, and hence, also require such limitation.

Applicant cites page 12, line 27 of the published PCT Application for support (Applicant's argument of 11/3/08, p. 9, paragraph 2). However, the cited publication is not of record. Moreover, page 12, line 27 of the certified PCT Application recites "inflammatory diseases, autoimmune, chronic and infectious diseases, including such", and as such does not meet the criteria of support for the generic limitation.

Applicant cites Example 4, which is specifically titled "Example 4: Development of tetraarginine formulations", and Tables 2 and 5 for support for the limitation (Id.). Moreover, these particle preparations were derived from subsets of experiments to optimize conditions. Specifically, Example 1 determines specific experiments that demonstrate that specific sugars and salts have differing influences on DNA yield, physical stability of DNA on particles (pp. 25-29), that precipitations using various ratios of protamine sulfate, EDTA, water, and either trehalose, sucrose, or lactose, provide for similar stability (pp. 29-31), although the actual data of stability is withheld, so the Examiner simply must take the word of Applicant that the stability is similar. However, the cited Example 4 recites in TABLE 2 a series of individual particles,

which are limited to gold, and precipitated with tetraarginine, in the presence of not only EDTA or DTPA, but also sucrose or trehalose. Moreover, the results in TABLE 2 only demonstrate that the control (spermine-condensed) generally provides a lower half-life at either temperature 35 or 40 deg C, however, at 40 deg C, DNA/trehalose/DTPA combination does worse than spermine, and this is the temperature that is claimed. Still further, the conditions of testing are not the conditions implied by the claims, which appears to imply in vivo. Simply put, there is nothing here to convince the Artisan that Applicant considered this to be the genera of particles which Applicant conveyed as their invention at the time of filing, much less the time of priority.

TABLE 5 is a hodge-podge of stabilities of various formulae at various temperatures, and hence, nothing can be gleaned here to determine that Applicant possessed this genera as the invention at the time of filing, much less the time of priority.

Still further, Applicant's own arguments appear to provide a post-filing mix-and-match analysis to provide disclosure to distinguish over the Art, which includes more than simply the temperature and half-life, but specific conditions of use of sugars, chelators, and length of protein which appears to argue for support. Such is simply an obviousness-type support meant to overcome art-supplied rejections, and obviousness simply does not provide for possession of the invention at the time of filing.

Lastly, the Examiner has reviewed the Application as filed and fails to find evidence that Applicant conveyed to the Artisan, either implicit or explicit, that the invention was limited the broad generic particles claimed, with the required properties.

Hence, these claims are properly rejected for comprising new matter.

Claim Rejections - 35 USC § 103 – Sanford/Balhorn (Oard)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 7, 12-13, 17-20, 22-30, 32, 37, 38, 42-45, and 67 remain rejected, and Claim 73 is newly rejected, under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,204,253 to Sanford, et al., and Balhorn, et al. (2000) Molecular Reproduction and Development, 56: 230-34, as evidenced by Oard (1993) Plant Cell, Tissue and Organ Culture, 33(3): 247-50, for reasons of record and as necessitated by amendment.

The reasoning is repeated for clarity of record, and the new claims are addressed:

With regard to Claims 1-3, 7, 13, 17-18, 25, 27, 28, 32, 38, 42-43 Sanford teaches M-10 series tungsten microprojectile particles (which range from 0.3 to 2.1 micrometers in diameter (e.g., Oard (1993) Plant Cell, Tissue and Organ Culture, 33(3): 247-50, p. 249, col. 1, paragraph 3), coated with DNA condensed in the presence of spermidine, and also in the presence of EDTA (e.g., col. 15, paragraph 2) and also in the presence of calcium chloride (e.g., Id.), and the methods of making claimed (e.g., Id.).

With regard to Claims 4-5, 28-29, Sanford teaches that a transgene for, *inter alia*, kanamycin resistance, is transformed into the cells, and further expressed (EXAMPLE 2). Kanamycin is a fungal protein, and hence, a Fungal antigen.

With regard to Claims 19-20, 44-45, the particles are subsequently contacted with ethanol (e.g., col. 15, paragraph 3).

With regard to Claims 22-24, Sanford teaches a needless syringe device, as it has no needle, but injects the particles into cells (e.g., Figure 1), and which contains a receptacle containing the particles for delivery (e.g., FIGURES 5a-5b).

With regard to Claim 26, Sanford teaches the addition of the spermidine to the mixture containing the microparticles and DNA (e.g., col. 15, paragraph 2).

However, with regard to all rejected claims, Sanford fails to teach the use of arginine of the formula $[Arg]_{2\text{-}10}$ or a physiologically acceptable salt thereof .

However, the purpose of spermidine in condensing the DNA is to provide compact particles, resistant to degradation, as taught in the Art by Balhorn, et al. (2000) Molecular Reproduction and Development, 56: 230-34, e.g., p. 230, paragraph bridging columns. Further, Balhorn teaches that transformations of somatic cells and sperm are improved by the faster release of the DNA from condensation by the use of small polymers of polyArginine, and specifically, for the highest change in off-rate, those between 6-12 arginines having the greatest release kinetics (e.g., p. 233, paragraph bridging columns). Still further, Balhorn teaches that by simply changing the amount of arginines in the polyArginine in such delivery methods, the length of time required to dissociate from the polyArginine could be tailored for each individual delivery system (e.g., p. 233, column 2, paragraph 2), and hence, tetraarginine (Claim 73) would be found upon routine experimentation.

Further, with regard to the presence of EDTA on the surface of the particle (e.g., Claim 67), absent reason to believe otherwise, these particles do have EDTA on their surface.

Hence, at the time of invention, it would have been obvious to modify the microprojectile particles of Sanford with the use of the polyarginines of Balhorn, to arrive at the claimed invention. The Artisan would have been motivated to do so to arrive at the desired release kinetics for any specific system. Moreover, the Artisan would have had a reasonable expectation of success, as Balhorn had already demonstrated the release kinetics to be improved.

Response to Argument – Sanford/Balhorn evidenced by Oard

Applicant's argument of 11/3/08 has been fully considered but is not found persuasive.

Applicant argues that (i) Sanford fails to teach or suggest the use of ARG(2-10) or salt thereof, and (ii) Sanford fails to address stability of its DNA coated particles or otherwise suggest any means for stailizing such (p. 10, paragraph 1).

Such is not persuasive. Sanford is not taken in a vacuum, but in the context of the Artisan and his/her knowledge and skill, and further, this is not a rejection based on anticipation, but on obviousness, and combined with the teachings of Balhorn, as further evidenced by Oard.

Applicant argues that Balhorn discusses only the stability of the protein/DNA complex, and not within the context of the precipitated protein/DNA on a gold particle, with regard to release kinetics (solubilization of the protein/DNA complex, versus release of the protein from DNA which is already in solution) (p. 10, paragraph 2).

Such is not persuasive. Balhorn provides a motivation for utilizing short polymers of polyArginine instead of spermidine, and further, provides specific motivation for experimenting with the specific size of the short polymer. Further, the motivation provided by the Examiner need not be the specific motivation provided by Applicant. However, with regard to the specific limitation as to the half-life of the particles, as noted in the modified rejection, above, the half-

life Applicant is quoting would appear to be a property which would be inherent in the particles, and which Applicant has only documented, rather than a truly unexpected and surprising result, and hence, absent reason to believe otherwise, these particles have the required half-life.

Applicant argues that Table 5 supports the fact that the Art-recognized precipitation of DNA/spermidine onto particles by CaCl2 only has a 3-day half life (TABLE 5, row 3), while particles formulated with Arg4 and no chelator have a half-life of 3.1 days (Id., row 6). Hence, it is argued that the Art-recognized methods do not achieve the results displayed. (p. 10, paragraph 3.)

Such is not persuasive. Applicant's argument is on the one hand that the polyArginine delivers the greater half-life and therefore Sanford's use of spermine cannot be modified with polyArginine because polyArginine provides the unexpected result, then, under the present argument that the chelator provides the increased half-life and that therefore, according the selective analysis made by Applicant's results, the chelator produces the results. Such arguments are not understood to be confluent, and negate each other. Is the invention the use of polyArginine, or the use a chelator? The Examiner has provided specific motivations to utilize both, and in combination. It would appear from the analyses that even in using spermidine (TABLE 2) 19 day delivery is obtained, while in other cases, the polyArginine may have a half-life well below 20 days. Further, given that the results even for spermidine may be so very close to 20 days (in which no statistical deviation analysis is provided), that it would appear that half-life under the particular conditions (which are not specific defined in the Examples) could easily be 20 days given any particular DNA/polyArg/precipitating agents. I.e., the result is simply a consequence of the particular conditions and reactants supplied, and within the experimentation

of the Artisan. Table 5, selectively analyzed appears to indicate that use of chelator increases half-life, however, Sanford already teaches the use of spermidine with chelator (see rejection above). Still further, if the particles on rows 3 and 6 of table 5 differ in terms of polyarginine versus spermine, it is apparent that polyArginine does not always contribute to increased half-life of particles and hence, it argues that any particular half-life is consequence of each component utilized, rather than any specific component. Hence, these results appear to be routine optimization of conditions, which is exactly what Applicant has presented in their examples. Applicant has optimized, in Example 4, tetraarginine formulations, as is evidenced by the title to the section. Hence, perhaps the issue is whether or not reporting of routine optimizations provides sufficient disclosure make something non-obvious. The Examiner does believe these results are surprising or unexpected, but simply a consequence of routine optimization. It should further be noted that Applicant's claims do not contain a requirement for the particular sugars utilized which appear to be required to produce these particles, and hence, Applicant's argument (and claims) that the EDTA/DTPA and polyArg is required is incommensurate with their own reported results, which requires precipitation in the presence of the particular sugars. Again the Examiner understands such to be routine optimization. Lastly, clearly Sanford teaches the use of EDTA and spermidine in the same precipitation of DNA onto microparticles (col. 15, paragraph 2).

Applicant analyses TABLE 5 to argue that short polymers of polyArg are providing an unexpected and surprising increased half-life to the particles (pp. 10-11, paragraph bridging).

Such is not persuasive. Applicant's own data shows that polyArginine does not necessarily provide any such increased half-life (e.g., TABLE 5: comparing rows 3 and 6, where the same half-life is obtained whether spermine or polyArg is utilized).

Applicant argues that adding a chelator provides a further increase in stability, and hence, it is also suprising and unexpected (pp. 10-11, paragraph bridging).

Such is not persuasive. Depending on conditions, the chelator may not even provide 20 days of half-life at 40 deg C (e.g., TABLE 2, last row). Further, each of these experiments contain various other sugars and conditions, and the particular conditions of the half-life are not even provided. Depending on the random system chosen, routine experimentation would provide for particles which last more than 20 days at 40 deg C. Lastly, the claims are drawn to those particles in the composition which are still suitable for use after 20 days; hence, because the decay rate will necessarily yeild some particles that are still suitable after 20 days, those particles still meet the claims.

Applicant argues that Adami, et al. (1998) J Pharm Sci, 87: 678-83 provides evidence that lysines failed to protect DNA from degradation as a condensing agent, and hence the Artisan would not have expected Arginine to work either (p. 11, paragraph 2).

Such is not persuasive. First, Applicant, contrary to their argument, has not supplied the cited Article with their response, and hence, it is not considered. Second, even if it should be shown that lysine fails to protect DNA from degradation when utilized as a condensing agent, such is not the motivation which is utilized to obviate the claims, and Applicant has not claimed anything with regard to protection from enzyme and sonication-induced degradation, and hence, such does not require any consideration.

Applicant argues that Sanford does not teach anything about half life and utilizes the particles on the same day as preparation. Further, Oard teaches that the microcarriers are utilized as soon as possible to avoid clumping, and that Balhorn fails to mention the use of arginine and chelator on its stability, as measured in days, and hence, the claims are not obvious.

Such is not persuasive. Applicant's claims do not require that the particles made are stored under particular conditions for 20 days, but only that the characteristic is present, such that IF it were stored in some system conditions at 40 deg C for 20 days, some particles would have survived and be suitable for delivery. Applicant has not claimed the composition after storage for 20 days, but simply those particles suitable for delivery, and the specific particles have a half-life of greater of than 20 days at 40 deg C, under any specific chosen conditions for the system. Oards decision to minimize clumping is simply irrelevant, as it says nothing about the half-life. Balhorn is not required to mention anything about half-life stability in any particular system within the claims, as it is not utilized for the teachings of chelators. Lastly, clearly Sanford teaches the use of EDTA and spermidine in the same precipitation of DNA onto microparticles (col. 15, paragraph 2).

Applicant rehashes arguments, saying that there is no basis to predict that long-term stability of the particles would be so high, again citing similar citations in Sanford, Oard, and Balhorn (p. 11, paragraph 3).

The same responses are made as above to each individual argument.

Applicant argues that Balhorn, by teaching dissociation rates and better cell entry kinetics, does not teach stability influences (pp. 11-12, paragraph bridging).

Such is not persuasive. Balhorn teaches another specific motivation to utilize polyArginine, and Applicant's own data argues that polyArginines have no influence on the stability (TABLE 5: compare rows 3 and 6). Further, as has been argued, the differences are miniscule and contradictive such that the Artisan would not determine any more from Applicant's tables but that any particular set of conditions and reactants produce particular stability results. Still further, to the point of implying that the off-rate of Balhorn suggests that the stability of the condensed DNA/protein on the microparticle would be would degrade faster, such is completely incorrect. The off rate of DNA/protein on the microparticle is essentially a solubilization of the DNA/protein, which must occur prior to the dissociation of DNA from the protein, and hence, the species involved negate the possibility of the off-rate from the protein to influence the off rate of the DNA/protein from the microcarrier.

In summary, Applicant's arguments amount to (i) the Art does not teach the use of polyArginine with a chelator to provide increased half-life; (ii) that the polyArginine provides unexpected results over the art-utilized spermine; and (iii) that the chelator further increases the half-life such that it provides further unexpected results. With regard to (iii), the Examiner argues that the use of the condensing agent (e.g., spermine) was known to be used in combination with EDTA to precipitate DNA onto microparticles for gene delivery (e.g., Sanford, Col. 15, paragraph 2). Hence, if EDTA provides the unexpected result, it is already taught in the Art. With regard to (ii), the Art teaches that if the condensing agent used is preferably polyArginine for its desireable release profile (e.g., Balhorn), and Applicant's own data indicates that polyArginine fails to provide any increased release kinetics when properly controlled (e.g., TABLE 5: compare lines 3 and 6). Hence, given the data, and given that polyArginine fails to

provide an unexpected result according to Applicant's own data, the distinct and valid motivation provide is enough to make the same particle, And the resultant particles' half-life is simply a consequence of the particular conditions and reactants used in the Art, and not the result of polyArginine. With regard to (i) the polyarginine provides for the desireability of polyArginines and chelators for specifically precipitating onto microparticles for DNA delivery. Hence, given that Applicant's data appears to indicate that the polyArginine is not necessarily going to produce the result written, and given that other components and the whole composition utilized appears to influence the particular half life, the Artisan would not be able to say more than the half-life is variable depending on the particular plasmid, protein, salts, chelators, sugars, and other reactants utilized, rather than that polyArginine and the presence of chelator is unexpected to produce such half life increases. Simply put, it the Examiner's position that the conditions are simply ones of routine experimentation, and hence the properties are a consequence of known and obvious methods. Still further, because the claim provides an undefined system, wherein the concentrations and pressure and volume and changes allowed therein are not defined, under any particular imaginary system, such result would be obtained. Still further, Applicant has not required that the system particles have a half-life of greater than 20 days, but simply that the half life is such that particles present after 20 days have experienced a half-life greater than 20 days (still not degraded at 20 days and therefore suitable for delivery), and those particles are claimed. Hence, under any particular storage, some particles will be left after 20 days, and those particles meet the claims.

Claim Rejections - 35 USC § 103, Sanford, Balhorn (Oard), Cherng

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 7, 12-15, 17-30, 32, 37-40, 42-46, and 67 remain rejected, and Claims 73, 79, 80, 82, and 83 are newly rejected, under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,204,253 to Sanford, et al., and Balhorn, et al. (2000) Molecular Reproduction and Development, 56: 230-34, as evidenced by Oard (1993) Plant Cell, Tissue and Organ Culture, 33(3): 247-50, as applied to claims 1-5, 7, 12-13, 17-20, 22-30, 32-38, 42-45, 67, and 73, above, and further in view of Oard (1993) Plant Cell, Tissue, and Organ Culture, 33(3): 247-50 and Cherng, et al. (1999) Pharmaceutical Research, 16(9): 1417-23, for reasons of record and as necessitated by amendment.

With regard to Claims 1-5, 7, 12-13, 17-20, 22-30, 32-38, 42-45, and 67, as is shown above, Sanford and Balhorn, as further evidenced by Oard, make obvious the various aspects of the claims.

However, Sanford and Balhorn, as further evidenced by Oard, do not make obvious the use of gold particles, further condensed in the presence of sucrose.

On the other hand, Oard teaches the use of gold particles can reduce particle clumping (e.g., p. 249, paragraph bridging columns). Further, Cherng teaches that condensation of nucleic acids with cationic polymers is further stabilized for storage by the presence of sucrose during the condensation (e.g., ABSTRACT).

With regard to Claims 79, 82, and 83, as shown in the above rejection, from Balhorn, it is routine experimentation to arrive at tetraarginine peptides, as well as heptaarginine peptides.

With regard to Claim 80, as shown above, it was known to conduct the precipitations on the microparticle in the presence of EDTA.

Hence, at the time of invention, it would have been obvious to modify the techniques of Sanford and Balhorn, as further evidenced by Oard, to use the gold particles of Oard to reduce clumping, and further to condense the DNA in the presence of sucrose as taught by Cherng, to increase the stability of the condensed DNA over time. Moreover, the Artisan would have had a reasonable expectation of success, as Oard teaches that gold particles will reduce clumping and Cherng taught that the sucrose present in the condensed solution would provide more stability.

Response to Argument – Sanford, Balhorn (Oard), Cherng

Applicant's argument of 11/3/08 has been fully considered but is not found persuasive.

Applicant argues that Sanford, Oard, and Balford, along with Cherng do not teach or suggest that the combination would confer a significant, non-additive stability, and as such, the particles are non-obvious (pp. 12-13, paragraph bridging).

Such is not persuasive. For the various reasons given above, it is argued that Applicant has not demonstrated unexpected results. Further, it is noted that nothing with regard to non-additive has been shown, and that if the Arginine polymer, as is shown, contributes nothing to stability, then there is nothing to add. Still further, the system of stability is undefined and any particular conditions are necessarily able to be found to produce such stability.

Applicant argues that Cherng does not utilize metal particles, but simply protein/DNA complexes and argues that Cherng's conclusion argues that the Artisan would not apply Cherng to other situations (p. 13, paragraph 2).

Such is not persuasive. Cherng demonstrates the increased stability which is produced. There is no reason to believe it would not apply to other situations. The cited conclusion simply implies that the results reported are for a particular situation, however, other situations, such as polyplexes and lipoplex formulations should work. Still further, the Art is repleat with demonstrations that sucrose, and for that matter other sugars like trehalose, stabilize proteins and other biomolecules, and hence, the Artisan would be aware that stability is simply increased by use of any sugar. While not required for the rejection, because the Artisan's skill encompasses such, the following are made of record, which demonstrate increased stability of various biologically-relevant molecules due to various sugars, and such stability measured by various stressors: (i) Ramos, et al. (1997) Applied and Environmental Microbiology (e.g., ABSTRACT); (ii) Ericksson, et al. (2003) Pharmaceutical Research, 20(9): 1437-43 (e.g., ABSTRACT); (iii) Kaushik, et al. (2003) Journal of Biological Chemistry, 278(29): 26485-65 (e.g., ABSTRACT); (iv) Garg, et al. (2002) Proceedings of the National Academy of Science, USA., 99(25): 15898-903 (e.g., ABSTRACT); (v) More, et al. (1998) Hindustan Antibiotics Bulletin, 40(1-4): 1-4 (ABSTRACT ONLY); (vi) Joshi, et al. (2001) AAPS PharmSciTech., 2(4): 25 (ABSTRACT ONLY), and Ruan, et al. (2003) European Journal of Biochemistry, 270: 1654-61 (e.g., ABSTRACT). Still further, this stabilizing force is even generally understood to be due to the changes in excluded volume and contact interaction with the surface protein, which is increased in the presence of sugars in general, and shown in Schellman (2003) Biophysical Journal, 85(1):

108-25, (e.g., ABSTRACT). Given this, it is clear that the Artisan would have understood that the molecules would be stabilized in the presence of various sugars, and particularly trehalose and sucrose. Therefore, Applicant's argument is not persuasive.

Applicant argues that Cherng does not overcome the deficiencies previous discussed with regard to Sanford, Balhorn, and Oard (p. 13, paragraph 3).

Such is not persuasive. Cherng is not required to overcome any deficiencies averred as it is found that there are no such deficiencies.

Claim Rejections - 35 USC § 103, Sanford, Balhorn (Oard), Cherng, Barman(Livesey)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7, 12-32, 37-46, 67-73, 76, 79, 80, 82, and 83 remain and/or are newly rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,204,253 to Sanford, et al., and Balhorn, et al. (2000) Molecular Reproduction and Development, 56: 230-34, as evidenced by Oard (1993) Plant Cell, Tissue and Organ Culture, 33(3): 247-50, and further in view of Oard (1993) Plant Cell, Tissue, and Organ Culture, 33(3): 247-50 and Cherng, et al. (1999) Pharmaceutical Research, 16(9): 1417-23, as applied to claims 1-5, 7, 12-15, 17-30, 32-40, 42-46, 67, 73, 79, 80, 82 and 83 above, and further in view of U.S. Patent Publication No. 2004/0142475 to Barman, et al, as further evidenced by U.S. Patent No. 6,194,136 to Livesey, et al., for reasons of record and as necessitated by amendment.

As shown above, Claims 1-5, 7, 12-15, 17-30, 32-40, 42-46, 67, 73, 79, 80, 82 and 83 are obvious over the Art cited, except the cited Art does not specifically teach the use of transgenes encoding therapeutic proteins, or the use of a combination of raffinose and sucrose to stabilize the DNA. Nor does the cited art teach or make obvious the transgenes encoding HPV, HIV, HSV2, HSV1 or Hepatitis B antigens.

On the other hand, Barman teaches that stabilizers such as saccharides may be used in combination to stabilize the nucleic acid protein complexes (e.g., paragraph 0054). Further, Barman teaches that HPV, HIV, HBV, and HSV (which includes HSV1 and HSV 2), antigens can be the transgenes for expression of antigens (paragraph 0036). Still further, Barman teaches influenza virus antigens to induce antibody responses (e.g., paragraph 0117). Still further Livesey also demonstrates the general understanding in the Art that various stabilizers which are sugars include raffinose (DESCRIPTION OF THE PREFERRED EMBODIMENTS, paragraph 29).

Hence, at the time of invention, it would have been obvious to modify the cited Art with Barman to use both raffinose and sucrose in stabilizing the particles and/or to use the various cited virus proteins. The Artisan would have been motivated to do so as the art already recognized that the sugars could be used in combination and/or the various proteins could be expressed for making antigens. Moreover, the Artisan would have had a reasonable expectation of success, as the Art already recognized the efficacious effect of saccharides.

Response to Argument – Sanford, Balhorn (Oard), Cherng, Barman(Livesey)

Applicant's argument of 11/3/08 has been fully considered but is not found persuasive.

Applicant argues that the newly added references fail to overcome the deficiencies of the previously-applied art (p. 14, paragraph 1).

Such is not persuasive. There are no deficiencies.

Applicant argues a failure to demonstrate surprising results (Id.).

Such is not persuasive. It is not agreed that these results are suprising but are simply due the results obtained under any particular reactants and conditions. In addition, the claims are not even commensurate with the surprising results, instead being drawn to any conditions which provide stability at 40 deg C for 20 days, and the resultant particles which survive and are suitable necessarily experienced a half-life beyond 20 days.

Claim Rejections - 35 USC § 103 – many references

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7, 12-32, 37-46, and 67-83 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,204,253 to Sanford, et al., and Balhorn, et al. (2000) Molecular Reproduction and Development, 56: 230-34, as evidenced by Oard (1993) Plant Cell, Tissue and Organ Culture, 33(3): 247-50, and further in view of Oard (1993) Plant Cell, Tissue, and Organ Culture, 33(3): 247-50 and Cherng, et al. (1999) Pharmaceutical Research, 16(9): 1417-23, and U.S. Patent Publication No. 2004/0142475 to Barman, et al, as further evidenced by U.S. Patent No. 6,194,136 to Livesey, et al., as applied to claims 1-7, 12-32, 37-46, 67-73, 76,

79, 80, 82, and 83 above, and further in view of the knowledge of the Artisan as evidenced by (i) Ramos, et al. (1997) Applied and Environmental Microbiology (e.g., ABSTRACT); (ii) Ericksson, et al. (2003) Pharmaceutical Research, 20(9): 1437-43 (e.g., ABSTRACT); (iii) Kaushik, et al. (2003) Journal of Biological Chemistry, 278(29): 26485-65 (e.g., ABSTRACT); (iv) Garg, et al. (2002) Proceedings of the National Academy of Science, USA., 99(25): 15898-903 (e.g., ABSTRACT); (v) More, et al. (1998) Hindustan Antibiotics Bulletin, 40(1-4): 1-4 (ABSTRACT ONLY); (vi) Joshi, et al. (2001) AAPS PharmSciTech., 2(4): 25 (ABSTRACT ONLY), Ruan, et al. (2003) European Journal of Biochemistry, 270: 1654-61 (e.g., ABSTRACT), and Schellman (2003) Biophysical Journal, 85(1): 108-25.

As shown above, the various references obviate the various claims, however, Claims 74, 75, 77, and 78 introduce the requirement of trehalose as the sugar, and the combination of gold particles precipitated with DNA in the presence of polyarginine, EDTA, and trehalose. Hence, the new aspect is essentially the use of trehalose.

However, as shown by the abstracts of (i) Ramos, et al. (1997) Applied and Environmental Microbiology, 63(10): 4020-25 (e.g., ABSTRACT); (ii) Ericksson, et al. (2003) Pharmaceutical Research, 20(9): 1437-43 (e.g., ABSTRACT); (iii) Kaushik, et al. (2003) Journal of Biological Chemistry, 278(29): 26485-65 (e.g., ABSTRACT); (iv) Garg, et al. (2002) Proceedings of the National Academy of Science, USA., 99(25): 15898-903 (e.g., ABSTRACT); (v) More, et al. (1998) Hindustan Antibiotics Bulletin, 40(1-4): 1-4 (ABSTRACT ONLY); (vi) Joshi, et al. (2001) AAPS PharmSciTech., 2(4): 25 (ABSTRACT ONLY), and Ruan, et al. (2003) European Journal of Biochemistry, 270: 1654-61, many sugars, and especially Trehalose is known to stabilize proteins, especially when the product is being dried. Still further, this

stabilizing force is even generally understood to be due to the changes in excluded volume and contact interaction with the surface protein, which is increased in the presence of sugars in general, and shown in Schellman (2003) Biophysical Journal, 85(1): 108-25, (e.g., ABSTRACT). Given this, it is clear that the Artisan would have understood that the molecules would be stabilized in the presence of various sugars, and particularly trehalose and sucrose.

Hence, it would be obvious to perform the various steps with trehalose, or really any particular sugar. The Artisan would do because it would allow increased stability to be imparted to the dried particles, and thereby allow their half-life to be increased. Moreover, the Artisan would have a reasonable expectation of success, as the Artisan knew that trehalose was efficient at stabilizing such.

Conclusion

No Claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ROBERT M. KELLY whose telephone number is (571)272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Robert M Kelly/
Primary Examiner, Art Unit 1633